Induction of immune tolerance to human embryonic stem cell-derived allografts

Grant Award Details

Induction of immune tolerance to human embryonic stem cell-derived allografts

Grant Type: Transplantation Immunology

Grant Number: RM1-01743

Project Objective: To induce immune tolerance to human embryonic stem cell-derived allografts

Investigator:

Name:	Yang Xu
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Immune Disease

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,192,680

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Induction of immune tolerance to human embryonic stem cell-derived allografts

Public Abstract:

Human embryonic stem cells (hESCs) can undergo unlimited reproduction and retain the capability to differentiate into all cell types in the body. Therefore, as a renewable source of various cell types, hESCs hold great promise for human cell replacement therapy. Significant progress has been made in establishing the conditions to differentiate hESCs into cells of therapeutic value. However, a major obstacle to the clinical application of these promising hESC-based therapies is the immune-mediated rejection of hESC-derived cells by the recipient because these cells express antigens that differ from those of the recipient patients. While rejection of grafts expressing different antigens can be delayed for a period of time if the recipient's immune system is persistently suppressed, most grafts are rejected eventually. In addition, persistent immune suppression also increases the risk for cancer and infection. Therefore, to develop hESC-based therapy, it is critical to develop effective approaches to induce immune tolerance to hESC-derived cells.

Extensive studies indicate that transplantation of donor's hematopoietic stem cells (HSCs) into the recipient prior to graft transplantation can induce tolerance of the recipient to the graft. Therefore, one promising approach that may be used to induce tolerance to hESC-derived cells is to transplant hESC-derived HSCs into the recipient. However, several bottlenecks hinder the evaluation of this promising approach. For example, due to the lack of specific markers for human HSCs, the differentiation and identification of hESCs into HSCs remains to be optimized. In addition, the animal model to study the human immune responses to hESC-derived cells remains to be established and validated.

To address these challenges, I have assembled a team of researchers with complementary expertise. We will genetically modified hESCs to improve our ability to identify and purify hESC-derived HSCs. In addition, we will develop humanized mouse models with functional human immune system to test whether transplantation of hESC-derived HSC and/or hESC-derived dendritic cells are sufficient to induce tolerance to hESC-derived cells such as cardiomyocytes. The ability to identify hESC-derived HSCs would facilitate the effort to provide a renewable cell resource for therapeutic bone marrow transplantation. In addition, our research could optimize the conditions to transplant hESC-derived HSCs in order to induce immune tolerance to differentiated cells derived from matched hESCs.

Statement of Benefit to California:

Limited therapeutic options are available for several devastating and costly diseases such as diabetes and heart diseases in California and our nation. In the case of diabetes, 1 of every 10 Californians (2.7 million) were afflicted with diabetes in 2007, costing the State $24.5 billion annually. Heart diseases remain the number one cause of death in California and nation, costing California even more than diabetes. Therefore, these diseases have devastating consequences on both those afflicted and on State/National healthcare costs. There remains an urgent and critical need for a cell-based cure of these diseases.

While significant progress has been made in the derivation of functional beta cells and cardiomyocytes from human ES cells, these allogenic cells will be rejected by the recipient upon transplantation unless the immune system of the recipient is persistently suppressed. However, immune suppression itself has severe consequences with significantly increased risk of cancer and infection. Therefore, it is critical to develop effective approaches to induce immune tolerance to hESC-derived cells. Our proposed research is aimed to develop approaches to induce immune tolerance to a wide range of hESC-derived cell types such as cardiomyocytes. The millions spent now on research is nominal when compared to the billions that will be saved in treatment costs and the improved quality of life for patients.